Remarks

The Official Action dated October 3, 2006 has been carefully considered. By the present amendment, independent claims 1 and 13 has been amended to clarify the inventive method examines weight loss during periods of energy imbalance by identifying gene expression during this period and comprises steps permitting comparison of the gene expression during this period with control gene expressions that permits distinguishing between the gene expression response to regulation of energy balance verses any gene expression response occurring as a result of the methodology, verses any gene response occurring as a result of differing nutrient load. In addition, the term "determining" is deleted in favor of the term "developing," and support for this substitution is found, for example, on page 2 lines 16-18, and on page 12, lines 5-7. Dependent claims are amended to comport with the added language. Support for these amendments is found throughout the specification, an in particular on pages 10 and 11 in the disclosure relating to Example 1. New claim 14 is added to define an embodiment comprising the novel inventive methodology directed to examining weight loss during a period of regulatory based weight loss following a prolonged overfeeding regimen, and the identification of gene expression during that period, thus providing new targets for treating body weight disorders relating specifically to perturbations in energy balance, as is disclosed throughout the present specification. As this amendment does not include new matter, entry is believed in order and is therefore respectfully requested.

Claims 1-14 are currently pending and subject to examination.

35 U.S.C. § 112, second paragraph, "definiteness"

Claims 1-13 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite. Specifically, the Examiner asserts that claims 1 and 13 are incomplete for omitting essential steps, such omission amounting to a gap between the steps and constituting "those steps required to obtain from the expression of a gene or a protein expression identified to determine a therapeutic strategy. The Examiner maintains that the metes and bounds of the term "therapeutic strategies" is unclear because it does not identify what the strategy is therapeutic for, and that the metes and bounds of the term "a prolonged overfeeding regimen" is unclear because "while the specification discloses specific embodiments, no specific definition is provided as to the minimal requirement of such overfeeding regimen encompasses." The Examiner notes that the specification defines at least 3 days as being the minimal period, "but in one embodiment, it is still unclear if the prolonged feeding regimen may encompass 1 day, 1 hour, or less."

The Examiner further asserts that claims 1 and 13 each recite "identifying gene and/or protein expression that occur...with the prolonged feeding regimen," however claim 4 limits the identification to occurring during and/or after the prolonged overfeeding regiment," such that the term "with" must be meant to encompass more than during or after the overfeeding regimen, which is inconsistent with the common meaning of the term "with."

These rejections are traversed and reconsideration is respectfully requested. Independent claims 1 and 13 are amended to delete the term "with" in relation to the overfeeding regimen. In addition, claims 1 and 13 have been amended to clarify that the methods relate to determining therapeutic strategies and/or targets for treating body weight disorders or wasting disorders, respectively, *by examining weight loss*. As presently disclosed, the relevant weight loss is that which occurs in response to a positive energy imbalance. Claims 1 and 13, as amended, recite the control groups as disclosed in the present specification as being necessary to making a

differential analysis of the gene expressions identified during the overfeeding regimen, or after termination of the overfeeding regimen, during the period of positive energy balance and weight loss.

With respect to the Examiner's concerns with lack of an express minimum for defining a "prolonged overfeeding regimen," Applicants note that the "prolonged feeding regimen is defined in the specification without regard to a minimum time, as this may vary with the size, base metabolism, activity level, feeding habits, and other individual characteristics of the selected experimental subjects so that a rigid definition fails to provide the flexibility to a practitioner as contemplated by the present invention. "Prolonged," therefore, according to the present invention, should be interpreted according to common understanding, that is, a duration in excess of normal, such that "normal" may be characterized on a group-by-group basis. Specific embodiments, wherein the regimen continues for periods ranging from 3 days upward are also disclosed, but it should be understood that the inventive methods may be tailored to the characteristics, including eating habits, of the experimental group without limitation as to a "minimum" that could only be derived from a species-specific or group-specific population response that may not be meaningfully applied to any group.

35 U.S.C. § 112, first paragraph "written description"

Claims 1-13 are rejected under 35 U.S.C. § 112, first paragraph as failing to comply with the written description requirement. Specifically, the Examiner states that claims 1-13 encompass the generic determination of a therapeutic strategy, while the specification discusses overfeeding and determining levels of gene or protein expression and that "therapeutic strategy" is merely referred to as using the methods. The Examiner asserts that the art teaches many

specific protocols for particular disorders which "may require various drugs and/or other nutrients and exercises," does not teach a generic therapeutic strategy or how to obtain one from the identification of a gene expression such that a practitioner in the art would not consider Applicants to be in possession of a generic method for determining a therapeutic strategy at the time of filing. This rejection is traversed and reconsideration is respectfully requested.

Independent claim 1, as amended, recites a method of developing therapeutic strategies and/or targets for treating disorders relating to body weight by examining weight loss, the method comprising: (a) establishing at least three groups of subjects; (b) administering a prolonged overfeeding regimen to a first group, administering a volume-matched infusion to a second group, and administering a volume-matched infusion to a third group; (b) terminating the prolonged overfeeding regimen to the first group, terminating the volume-matched infusions to the second group and terminating the volume-matched infusions to the third group; (c) providing free access to food to the first group, providing free access to food to the second group, and providing pair-fed access to food to the third group, wherein the third group is pair-fed with the first group; (d) identifying gene expression in the first group, identifying gene expression in the second group, and identifying gene expression in the third group, and; (e) subjecting the gene expressions to an analysis. The recitation of independent claim 13 is similar except that it relates to developing therapeutic strategies and targets for treating wasting disorders.

Both claims have been amended to replace the subjectively stronger "determining" with "developing," which makes to clear that the present inventive methods, directed to the study of weight loss, specifically the weight loss associated with regulatory mechanisms that are triggered by a positive energy balance, provide the practitioner with a novel approach to the development of strategies and targets for treating body weight disorders, because known methods derive from

studies of the obese state or the wasted state, or over-consumption/under-consumption of calories, without concern for the role of energy imbalance. (Please note that support for this term substitution is found expressly, for example, on page 12, lines 5-8, of the instant specification.) The present inventive methods seek to provide the practitioner with a novel methodological tool for developing strategies and targets capable of employing or impacting energy balance regulatory mechanisms, via genes expressed in response to perturbations in energy balance, to treat body weight disorders.

The written description requirement requires that claim recitations be supported by the specification such that the scope of the claim is commensurate with the scope of support. As amended, the scope of the instant independent claims is clear, and disclosure of specific strategies or targets or agents efficacious for treating body weight disorders is irrelevant to that scope. Hence, Applicants submit that the written description requirement as applied in the instant case does not require disclosure in the specification of specific therapies or agents for treating body weight disorders.

Hence, the rejection of claims 1-13 under 35 U.S.C. § 112, first paragraph for failing to comply with the written description requirement has been overcome. Reconsideration is respectfully requested.

13 U.S.C. § 112, first paragraph, enablement

Claims 1-13 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. Specifically, the Examiner asserts that claims 1-12 encompass a method of determining any therapeutic strategy, determining any target for examining any weight loss, any prolonged overfeeding regimen, any identification at any time, and determining

gene expression in any animal, and that claim 13 parallels claim 1 but requires the targets to be for wasting disorders rather than weight loss. The Examiner asserts the nature of identification of a therapeutic strategy is necessarily not reasonably predictable and that identification of expression of a gene in an individual would require further experimentation to determine how to use such a gene in any particular strategy to effect any particular therapeutic strategy, examination of weight loss, or to effect or counteract any particular wasting disorder in any particular animal.

The Examiner suggests that the present claims require the mere identification of gene expression and not a controlled determination of changes in gene expression due to overfeeding, and that "because Applicants claims do not require a controlled comparison of gene expression levels to unaffected individuals, it is not reasonably predictable that any particular gene obtained would be correlated to overfeeding, much less any therapeutic strategy, etc. The Examiner discusses, at length, the proposition that "gene association studies are not reasonably predictable of any particular marker of any particular disease" and uses research and failed clinical applications of leptin for illustrative purposes.

The rejection is traversed and reconsideration is respectfully requested.

The recitations of independent claims 1 and 13 are set forth in detail above. Applicants draw attention to the added language that details the control groups, which, in turn, enables the differential analysis of gene expression that provides targets with a reasonable expectation that the targets will be specific to weight loss relating to regulatory mechanisms triggered in response to a positive energy balance. This additional language overcomes the Examiner's objections to lack of specificity of the gene expression due to lack of implementation of appropriate controls,

and confers the requisite predictability as to whether analysis of the identified gene expression will yield information useful in developing therapeutic strategies and targets for treating body weight disorders.

Applicants further note that the present specification provides guidance as to therapeutic strategies that would be usefully developed in response to an empirical finding that gene expression reflects a bias to consume more or less food on the basis of an energy imbalance versus other bases (see page 7, lines 5-18, e.g.).

The Examiner appears to argue that undue experimentation would be required to identify specific targets having efficacy with respect to specific treatments and agents. Applicants submit, however, that this describes elements of another invention and note that the section 112 enablement requirement merely provides that the specification must enable one skilled in the art to "use" the invention. The present invention relates to methods for developing therapeutic strategies or targets for treating disorders relating to body weight, and provides methods that may be practiced with a reasonable expectation of success of generating genetic expression data that enables the practitioner to develop therapies and targets specific to treating body weight disorders resulting from perturbations in energy balance rather than nutrient load, per se, or body weight, per se, as do methods known in the art.

Hence, the present inventive methods are enabled and the rejection of claims 1-13 under 35 U.S.C. §112, first paragraph, for enablement has been overcome. Reconsideration is therefore respectfully requested.

35 U.S.C. § 102

Claims 1, 4, 6-8 and 9-13 are rejected under 35 U.S.C. §§ 102(a) and 102(e) as being anticipated by U.S. Patent Publication No. 2002/0041870 to Wu, which claims priority to July 26, 2000. Specifically, with regard to claims 1, 4 and 13, the Examiner asserts that Wu teaches identification of differentially expressed genes in the hypothalamus due to overfeeding regimens illustrated in Example 1, and also teaches various methods for producing overfed animals by providing diets over 100% of a normal diet. The Examiner further asserts that Wu describes identifying gene expression in the hypothalamus. With regard to claim 9, the Examiner asserts that Wu teaches isolation of RNA and analysis of the levels of expression of the RNA, and that the RNAs expressed are selected based on the level of expression, "which necessarily defines the target." With regard to claims 11-12, the Examiner asserts that Wu's specific example "is inherently a statistical analysis of the expression differences of RNAs in the hypothalamus. This rejection is traversed and reconsideration is respectfully requested.

Independent claim 1 recites a method of developing therapeutic strategies and/or targets for treating disorders relating to body weight by examining weight loss, the method comprising: (a) establishing at least three groups of subjects; (b) administering a prolonged overfeeding regimen to a first group, administering a volume-matched infusion to a second group, and administering a volume-matched infusion to a third group; (b) terminating the prolonged overfeeding regimen to the first group, terminating the volume-matched infusions to the second group and terminating the volume-matched infusions to the third group; (c) providing free access to food to the first group, providing free access to food to the second group, and providing pair-fed access to food to the third group, wherein the third group is pair-fed with the first group; (d) identifying gene expression in the first group, identifying gene expression in the second group, and identifying gene expression in the third group, and; (e) subjecting the gene expressions to an

analysis. Independent claim 13 recites a method of developing therapeutic strategies and/or targets for treating wasting disorders, the method comprising a method similar to that recited in independent claim 1.

Wu, on the other hand, discloses methods and compositions related to treating obesity, but focuses on discovery and manipulation of obesity-specific genes and polypeptides. Wu is not concerned with differential therapeutic approaches or analysis of genetic expression data in order to treat a presenting body weight disorder according to its origin, for example, a body weight disorder that arises from perturbations in energy balance. Wu merely identifies genes and polypeptides associated with the state of obesity, then develops interventions aimed at targeting those genes and polypeptides.

With respect to Wu Example 1 asserted by the Examiner as containing the anticipating disclosure, Wu actually discloses a method of searching for "obesity-related novel target genes." The method comprises analysis of mRNA expression in the hypothalamus in obese rats where the obesity resulted from a high fat diet, compared only with mRNA expression in the hypothalamus' of lean rats on a normal diet. Wu teaches use of high-fat diet induced obesity rather than obesity resulting from a prolonged overfeeding regimen according to the present methods. There is no control in Wu for the difference in genetic expression that may result merely from the differing nutrient load, apart from the obesity, as exists in the present inventive methods.

Wu teaches a single control for comparison purposes against lean rat cDNA libraries. Wu discusses generation of up-regulated genes under this paradigm. Applicants submit that Wu actually illustrates the deficiencies in methodology sought to be overcome by the present

invention. The genetic up-regulation observed by Wu cannot be correlated, necessarily, to either obesity or to energy balance, or to nutrient load, or to any particular origin of the body weight disorder. Wu seeks genetic expression correlates to obesity, per se. The present invention provides a method to obtain genetic expression correlates to weight loss occurring as a result of a positive energy imbalance. Clearly these are very different methodologies for developing strategies and targets for treatment of body weight disorders.

Anticipation under 35 U.S.C. § 102 requires the disclosure in a single prior art reference of each element of the claims under consideration, *Alco Standard Corp. v. TVA*, 1 U.S.P.Q.2d 1337, 1341 (Fed. Cir. 1986). Wu fails to teach or otherwise disclose methods of developing therapeutic strategies and/or targets for treating disorders relating to body weight, comprising, as required by the instant independent claims, employment of a prolonged overfeeding regimen to achieve a subject group having a positive energy balance and identification of gene expression during the period of positive energy balance, including during the period of weight loss that occurs in response to a positive energy balance, controlled for both methodological and nutrient load concerns. Hence, the rejection of instant claims 1, 4, 6-8, and 9-13 under 35 USC § 102 over Wu is overcome. Reconsideration is respectfully requested.

35 U.S.C. § 103

Claims 1-3 and 5 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Wu, and Hagan, et al. (1999) J. Neuroscience, 19(6): 2362-67. Specifically, the Examiner relies on the teachings of Wu set forth above, and notes that Wu fails to teach the method of overfeeding using a gastric catheter or the measurement of levels of gene expression prior to the overfeeding. The Examiner asserts that Hagan teaches use of a gastric catheter in overfeeding regimens in

analyzing CNS RNA levels, which includes the hypothalamus, and that Hagan further teaches that expression levels obtained prior to the overfeeding regiment may be used. This rejection is traversed and reconsideration is respectfully requested.

The recitation of independent claim 1 is set forth in detail above.

As established in the prior argument over the § 102 rejection, Wu fails to teach or disclose the presently inventive methods. In addition, Applicants submit that Wu fails to suggest the present inventive method as defined by instant claim 1. Specifically, Wu fails to teach or suggest employment of a prolonged overfeeding regimen, but, rather, relies on high dietary fat to generate an obese experimental population. As Applicants noted previously, there may be contributions to the genetic up-regulation or down-regulation observed in the Wu obese subjects based on nutrient load. In fact, it is likely that the genetic expression observed in response to weight gain from a high fat diet differs from the genetic expression observed in response to prolonged overfeeding according to the present methods. Unlike the present inventive methods, within the paradigm itself, Wu fails to control for differences in nutrient load, and, significantly, Wu's methods are directed to gene expression solely in response to obesity, and not in response to the perturbations in energy balance, as taught by the present inventors.

According to the present invention, gene expression may be identified during the overfeeding, and subsequent to the overfeeding. In the latter context, the subject may be eating less in response to regulatory mechanisms triggered by the positive energy balance. The saliency of this data is established by use of a control group, as currently recited, to account for any differences in genetic expression during the weight loss period that may be due specifically to the different nutrient loading. Once nutrient load is controlled, the gene expression in the

positive energy balance subjects may be more cleanly correlated to the energy balance regulation.

Wu is not concerned with therapeutic strategies or development of targets based on energy balance regulation, but is interested in gene expression and generation of potential targets based on correlates to obesity, per se. Wu does not teach or suggest identification of gene expression during a post-overfeeding period comprising weight loss by the previously over-fed but now freely fed subjects. The secondary reference, Hagan, similarly is not concerned with studies or characteristics of weight loss or regulation of energy balance, or the gene expressions associated therewith, and therefore does not overcome the deficiencies of the primary reference.

To establish prima facie obviousness of the claimed invention, all the claim limitations must be taught or suggested by the prior art, *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (CCPA 1974). Furthermore, references relied upon to support a rejection under 35 U.S.C. §103 must provide an enabling disclosure, i.e., they must place the claimed invention in the possession of the public, *In re Payne*, 203 U.S.P.Q. 245 (CCPA 1979). The combination of Wu and Hagan fails to teach or disclose methods which, inter alia, analyze gene expression in response to perturbations in energy balance, as reflected in the inventive methods defined by the present independent claims. The combination of Wu and Hagan discloses the state of obesity alone as the antecedent to the relevant gene expression, and does not disclose methods which measure gene expression during periods of activation of regulatory mechanisms triggered by energy imbalances according to the present invention. Hence, the rejection of claims 1-3 and 5 under 35 U.S.C. § 103 over Wu in view of Hagan is overcome. Reconsideration is therefore respectfully requested.

Claims 1 and 9-10 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Wu, and Rast et al. (2000) Dev. Biol. 228: 270-86. Specifically the Examiner asserts that Wu anticipates, and therefore renders obvious, claims 1 and 9 as per the §102 rejection analysis set forth in detail above. The Examiner further notes that although Rast does not teach the making of a probe array prepared from the RNAs and using such to analyze RNA expression, Wu recognizes that any method of high-throughput analysis may be used. This rejection is traversed and reconsideration is respectfully requested.

The recitation of independent claim 1, and the teachings of Wu as relied upon by the Examiner, are set forth in detail, supra.

Once again, Applicants note that Wu fails to teach or suggest the methods embodied by present independent claim 1. As noted in the prior §103 traversal, Applicants claims are drawn to methods for developing therapeutic strategies and novel targets based on identification of gene expression correlating to regulation of energy balance during periods of weight loss after prolonged overfeeding, such periods being induced by the involuntary overfeeding and resulting restorative efforts by energy balance regulatory mechanisms, heretofore unexploited as according to the present inventive methods. Rast, which is directed to new technologies for isolating differentially expressed genes from large arrayed cDNA libraries, may, indeed, be usefully employed in practicing certain aspects of the present methods, but does not overcome the deficiencies of the primary reference, Wu. Rast is completely devoid of teachings related to obesity, body weight regulation or methodologies relating to gene expression correlating to weight loss or weight gain, and is otherwise inapposite to the substantive subject matter of either the present invention or Wu, and irrelevant, therefore, to the substantive deficiencies of Wu.

Hence, the rejection of claims 1 and 9-10 under 35 U.S.C. §103 is overcome and reconsideration is respectfully requested.

Applicants believe this is a comprehensive response to the rejections of claims 1-13 under 35 U.S.C. §§ 102, 103 and 112 as set forth by the Examiner in the October 3, 2006 office action. Applicants respectfully submit that the present application is in condition for allowance. The Examiner is encouraged to contact the undersigned to resolve efficiently any formal matters or to discuss any aspects of the application or of this response. Otherwise, early notification of allowable subject matters is respectfully solicited.

Respectfully submitted,

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